Editorial

Matching treatment to the genetic basis of (lipid) disorder in patients with coronary artery disease

Most people of old age in the western society have atherosclerosis to a greater or lesser extent; the condition can almost be regarded as a normal consequence of aging.[1] Therefore, the clinical problem of atherosclerosis may be better described by the term "accelerated" atherosclerosis, which reflects the fact that some patients suffer earlier than most from an atherosclerotic process. It is this acceleration of atherosclerotic disease progression that is usually the subject of investigation.

Establishing the rate of progression of coronary atherosclerosis in patients is important as progression of the disease is one of the major factors that determines clinical prognosis.[2 3] Therefore, identifying patients at risk for increased progression of coronary artery disease (CAD) is important as these patients might benefit from early (lipid lowering) treatment. Thus far, it has proved difficult to identify patients at increased risk when lipoprotein disturbances are moderate, which is the case for most patients seen in daily practice.

Another problem is that, although lipid lowering appears to retard progression of coronary atherosclerosis, not every patient benefits to the same extent from treatment—for example, in spite of intensive low density lipoprotein (LDL) cholesterol reduction and high density lipoprotein (HDL) cholesterol augmentation, a substantial percentage of the treated patients in the familial atherosclerosis treatment study,[4] experienced progression of coronary atherosclerosis over 2.5 years. Even the introduction of a powerful class of lipid lowering agents, HMGCoA reductase inhibitors or "statins", has not led to complete control of progression and its clinical sequelae.[5 6]

Consequently, we have two problems to face: how to identify patients at increased risk for progression of CAD; and how to determine which of these patients will benefit from (lipid lowering) treatment.

Molecular cardiology as possible solution

A clue to the solution of both problems may be found in the rapidly growing field of molecular cardiology. It is well known that a family history of CAD is associated with increased risk for development of CAD and its clinical sequelae. Studies in twins have revealed a greater genetic risk in monozygotic than dyzygotic twins, and adoption studies have shown that most of the excess risk is genetic rather than environmental. However, the mechanisms through which a family history of CAD increases risk is still largely unknown. Many aspects of coronary atherosclerosis appear to be under genetic control. Where do we stand now, more than 100 years after the death of Gregor Mendel (1822–84), by many considered a founding father of modern genetics. Many genes have been identified and studied to determine whether they are related to the development of CAD. Some monogenetic disorders may induce premature atherosclerosis, other genetic alterations cooperate in a polygenetic model, modifying the process of atherosclerosis. Furthermore, genetic alterations may modify not only disease but may also the efficacy of treatment.

How far are we in identifying genetic factors involved in the progression of coronary atherosclerosis and the response to cholesterol lowering drugs? Certainly we do not have all the answers yet. This editorial uses illustrations in two fields to show how far we have come: the increased progression rate of CAD; and restenosis after percutaneous transluminal coronary angioplasty (PTCA).

Increased progression of CAD

It has proved difficult to identify patients at increased risk for increased progression of CAD when lipoprotein disturbances are moderate. Therefore, recently research has been initiated to study the nature and frequency of gene mutations/variations in individuals with CAD and subtle combined hyperlipidaemia. Such a subtle combined hyperlipidaemia can for instance be caused by a mutation in the lipoprotein lipase (LPL) gene, as LPL is an important lipolytic enzyme of triglyceride rich lipoproteins, which are considered to be atherogenic. Indeed, it has been shown that heterozygosity for such a mutation (LPL Asp9Asn mutation), which causes only subtle changes in fasting plasma lipids, promotes progression of coronary atherosclerosis and diminishes clinical event free survival (fig 1).[7] The deleterious effects of the mutation could be totally reversed by statin treatment.

Recently, a significant relation was described between variation (polymorphism) at the cholesteryl ester transfer protein (CETP-Taq1b) gene locus and the progression of coronary atherosclerosis. CETP is involved in HDL cholesterol metabolism/reversed cholesterol transport and thus may be involved in the atherosclerotic process. This common CETP gene variant (polymorphism) appeared to predict, independent of plasma HDL cholesterol, whether men with CAD would benefit from lipid lowering treatment to delay the progression of coronary atherosclerosis.[8] Patients at high risk of progression (b1/b1 genotype) largely benefited from pravastatin, patients at intermediate risk of progression (b1/b2 genotype) had intermediate benefit, whereas patients at low risk of progression (b2/b2 genotype), 16% of cases, had no apparent benefit from

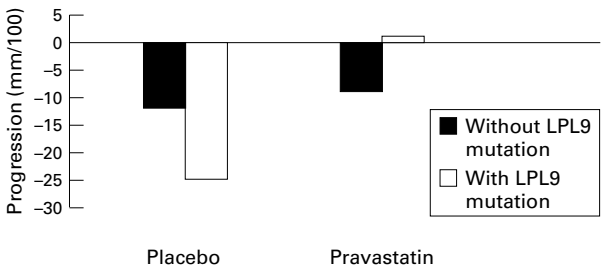

Figure 1 Influence of the Asp9Asn lipoprotein lipase (LPL) mutation on progression of coronary atherosclerosis. The bars show progression of coronary atherosclerosis, expressed as decrease in minimum obstruction diameter (MOD). Note that in the placebo group patients carrying the mutation have an extraordinary high progression rate compared to non-carriers ($p = 0.028$), whereas this is totally abolished in the pravastatin group (interaction test for differential effect of mutation − randomised therapy $p = 0.055$), suggesting that carriers of the mutation are very sensitive to pravastatin treatment.

pravastatin with regard to disease progression, suggesting that this last group might be better off with a different or even no medical intervention.

Restenosis after PTCA

Identification of patients at high risk of restenosis is important, because these patients might benefit particularly from early lipid lowering treatment or another treatment modality besides PTCA, such as stenting or coronary artery bypass grafting. An association has been found between the insertion/deletion (I/D) polymorphism of the angiotensin converting enzyme (ACE) gene and (in stent) restenosis.[9 10] This concept is valid as tissue proliferation is observed in recurrent lesions, ACE is a factor of smooth muscle cell proliferation and plasma ACE is largely controlled by ACE I/D polymorphism of the enzyme gene. Other candidate polymorphisms of genes to be associated with the process of restenosis are those to be found in genes that code for matrix metalloproteinases (MMP) as MMPs are involved in connective tissue turnover in the vessel wall and are active in wound healing processes, both features of the process of restenosis. For a variant of the MMP-3 (stromelysin-1) gene such an association with clinical restenosis leading to repeat PTCA has been demonstrated.[11]

The consequence of these findings might be that the genetic status of the patient could be checked before PTCA and the results used to guide treatment—for example, preferably stents not used for patients with the ACE D/D genotype. It should be emphasised that we need trials to turn these concepts into practice and to prove their validity.

Perspectives

From these results we might conclude that, in the near future, assessment of genetic factors will identify patients at high risk for progression of CAD and restenosis after PTCA, thereby allowing a timely and optimal therapeutic strategy. However, some words of caution seem appropriate. The findings described here are just associations not directly proving a causal relation between a genetic variation and disease characteristics. The ACE I/D polymorphism has been implicated in over 20 disease conditions and it is not likely that all the described associations reflect causal relations. This illustrates the complexity of polygenic, multifactorial diseases. In a beautiful editorial Rosenthal and Schwartz described some criteria to be met in establishing medically useful links between genetic variations and disease.[12] First, the change in the gene must cause a relevant alteration in the function or level of the gene product (which is always a protein). Second, the beneficial and harmful phenotypes must have apparent clinical differences. Third, the hypothesis linking the genotype to disease must be convincing, and fourth, the number of cases linking a genotype to disease must be sufficient. Finding the specific genetic and environmental components that are of relevance in a gene–environment interaction causing disease is not an easy task, but we are making progress.

In conclusion, genetic factors in atherosclerosis can be viewed to act on the level of causing or modifying disease as well on the level of modifying the effects of treatment. The dissection of the rapidly growing number of genetic variations will thereby surely reverse the treatment of cardiovascular disorders from a population based approach towards tailored treatment to fit individual risk profiles.

J WOUTER JUKEMA
Cardiology Division, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, Netherlands

1 White NK, Edwards JE, Dry TJ. Relationship of degree of coronary atherosclerosis with age, in men. *Circulation* 1950;**1**:645–54.
2 Buchwald H, Matts JP, Fitch LL, *et al*, for the Program on the Surgical Control of the Hyperlipidemias (POSCH) Group. Changes in sequential coronary arteriograms and subsequent coronary events. *JAMA* 1992;**268**: 1429–33.
3 Waters D, Craven TE, Lespérance J. Prognostic significance of progression of coronary atherosclerosis. *Circulation* 1993;**87**:1067–75.
4 Brown G, Albers JJ, Fisher LD, *et al*. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;**323**:1289–98.
5 MAAS Investigators. Effect of simvastatin on coronary atheroma: the multicentre anti-atheroma study (MAAS). *Lancet* 1994;**344**:633–8.
6 Jukema JW, Bruschke AVG, van Boven AJ, *et al*. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The regression growth evaluation statin study (REGRESS). *Circulation* 1995;**91**:2528–40.
7 Jukema JW, Van Boven AJ, Groenemeyer B, *et al*. The Asp9 Asn mutation in the lipoprotein lipase gene is associated with increased progression of coronary atherosclerosis. *Circulation* 1996;**94**:1913–18.
8 Kuivenhoven JA, Jukema JW, Zwinderman AH, *et al*. The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. *N Engl J Med* 1998;**338**:86–93.
9 Amant C, Bauters C, Bodart JC, *et al*. D allele of the angiotensin I-converting enzyme is a major risk factor for restenosis after coronary stenting. *Circulation* 1997;**96**:56–60.
10 Ribichini F, Steffenino G, Dellavalle A, *et al*. Plasma activity and insertion/deletion polymorphism of angiotensin I-converting enzyme. A major risk factor and a marker of risk for coronary stent restenosis. *Circulation* 1998; **97**:147–54.
11 de Maat MPM, Jukema JW, Ye S, *et al*. Effect of the human stromelysin-1 promoter on pravastatin treatment in coronary atherosclerosis and restenosis. *Am J Cardiol* 1999;**83**:852–6.
12 Rosenthal N, Schwartz RS. In search of perverse polymorphisms. *N Engl J Med* 1998;**338**:122–4.